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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,181	10/16/2001	Haruki Yamada	SHIM1110	6530

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,181	YAMADA ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005 and 15 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *10-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Applicant's amendments filed March 28, 2005 and April 15, 2005 are acknowledged and have been entered. Claims 1-16 are pending. Claims 1-9 and 16 are under examination. Claims 10-15 are withdrawn from consideration, being drawn to a non-elected invention.

2. The objections to the specification for containing minor informalities are withdrawn in view of Applicant's amendments. The objection to claims 2-9 for lacking literal antecedent basis is withdrawn in view of Applicant's amendment. The rejection of claims 1-9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 112

3. Claims 9 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine preparation for influenza, rotavirus, measles virus, rubella virus, mumps virus, *Bordetella pertussis*, and diphtheria bacillus, does not reasonably provide enablement for a vaccine preparation for *Helicobacter pylori*, AIDS virus, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosome. This rejection was previously applied to claim 9 only, however, in view of new claim 16's subject matter, claims 9 and 16 are rejected. The rejection is set forth below as in the previous Office action. Applicant's arguments are addressed in the next paragraph (4).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with

these claims. The breadth of the claims encompasses a vaccine for each of the microorganisms listed in claim 9. A vaccine is a preparation of killed or weakened microorganisms that induce a protective immune response in the recipient. The recipient is then protected upon subsequent challenge and disease is prevented. The claims encompass protective immunity against microorganisms for which there are no vaccines available. The nature of the invention is vaccination against pathogenic microorganisms (bacteria, viruses and parasites). The state of the art reveals that there are no vaccines available for the following pathogens: *Helicobacter pylori*, AIDS virus (HIV), enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosomes. The following are cited as evidence of the lack of vaccines for these microorganisms:

- *Helicobacter pylori (H. pylori)*. Michetti (*Gut*, 1997, 41:728-730) discloses the advances and challenges in the search for a *H. pylori* vaccine. Current treatment is antibiotics and is in no way preventative. Vaccination of mice with the VacA cytotoxin and urease has shown protective responses, but the application to humans will require a greater understanding of the type of immune response required for protection (page 729, first column, paragraphs 2 and 3).
- Enterohaemorrhagic *E. coli* (EHEC). Li *et al.* (*Infection and Immunity*, Sept. 2000, 68(9):5090-5095) disclose that there is currently no vaccine for EHEC (abstract). There is no good animal model for EHEC pathogenesis (page 5090, second column, beginning of last paragraph). Li *et al.* demonstrate that there is a strong immune response among human patients to the Tir virulence factor of EHEC, but there is not enough information for its use as a vaccine candidate yet (page 5094, last paragraph).

- *Chlamydia*. Lu *et al.* (*J. Immunol.* 2002, 169:6324-6331) disclose vaccination of mice with inactivated whole cell *C. trachomatis* (mouse pneumonitis, mouse model) in combination with GM-CSF as an adjuvant (abstract). Without the GM-CSF, the mice exhibited no protective response against challenge. However, with the adjuvant, mice exhibited enhanced cellular and humoral immune responses to homologous challenge. The findings of Lu *et al.* have implications on the development of a vaccine for humans.
- *Mycoplasma.* Mycoplasmas are currently treated with antibiotics, however, no vaccine currently exists for humans. Duffy *et al.* (*J. Antimicrobial Chemotherapy*, 2000, 45, Suppl. S1, pages 29-33) disclose antibiotic treatments for mycoplasmas, which is the current state of the art treatment.
- *Plasmodium.* The Centers for Disease Control (CDC) fact sheet about malaria, discloses that there is no vaccine approved for human use (page 3, "Preventing Malaria" subheading) because the life cycle of the parasite is very complex, displaying different antigens at different times. Current treatment for parasites is drugs.
- *Coccidium.* The MayoClinic fact sheet on Toxoplasmosis (*Toxoplasma gondii*, an intestinal coccidium) discloses that the disease is treatable with drugs, but there is no vaccine (page 1, see "Overview").
- Schistosome. The CDC fact sheet about Schistosomiasis discloses that the parasitic infection is treatable with drugs, but there is no vaccine for the parasite because of its complex life cycle and varied antigen display.

The level of skill in the art regarding vaccination is high. The level of predictability in the art with regard to vaccination of viruses and bacteria is low because of the complexities of microorganisms and the human immune response. The amount of guidance in the specification is limited to a listing on pages 12-13 of bacterial and viral vaccines, some of which are enabled, and some of which are described generally in terms of antigens or whole cell/virus preparations. The amount of guidance provided for *mycoplasma*, HIV and *H. pylori* does not specifically teach which antigens are useful for vaccination. The working examples are drawn to influenza, pertussis-diphtheria-tetanus combined vaccine, Hepatitis B, measles, rubella and mumps (all recognized vaccines). Other working examples include Japanese encephalitis virus and *mycoplasma*, showing induction of an immune response. It would require undue experimentation to discover the antigens or cell/virus preparations required to induce a protective immune response for the claimed microorganisms *Helicobacter pylori*, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosomes. Given the breadth of the claims, the nature of the invention, the state of the art, the high level of skill in the art, the low level of predictability in the art, the limited guidance in the specification and working examples, and the undue amount of experimentation required to discover vaccine preparations of various microorganisms, the claims are not enabled for their full scope.

4. Applicant's arguments regarding the rejection under 35 U.S.C. 112, first paragraph, for lack of enablement, have been fully considered but fail to persuade withdrawal of the rejection. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that the Office's definition of "vaccine" is too narrow, being directed only to preventative vaccines. Applicant's definition of vaccine also includes treatment vaccines. In view of the broader definition of vaccines, which include preventative as well as treatment vaccines, the claims should not be rejected for reading only on preventative vaccines.
  - In response, the Office acknowledges that Applicant's definition of vaccine is meant to encompass both prevention and treatment. However, without clarification in the claims, one would not know which definition Applicant's intends: prevention or treatment. Given that the same term is intended to have two different definitions, the claims must clarify what is actually meant by the term "vaccine". Lacking clarification that the term "vaccine" means treatment only and not prevention when referring to the non-enabled pathogen compositions, the claims remain non-enabled for vaccines.
- Applicant argues that vaccines for the alleged non-enabled vaccines have been developed prior to the filing date of the instant application. Applicant points to several references that disclose vaccines for *Helicobacter pylori*, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosomes.
  - In response, the Office recognizes that the prior art literature refers to "vaccines" for the above-listed organisms. However, these vaccines did not provide complete protection against humans. Applicant's claims are drawn to a vaccine composition, which means that the vaccine must confer complete preventative protection against the named pathogen. The prior art has not demonstrated the

ability to complete prevent infections of *Helicobacter pylori*, HIV, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosomes in humans. Therefore, the prior art cannot be relied upon to prove that vaccines for *Helicobacter pylori*, HIV, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosomes were enabled at the time of the instant invention.

Claim Rejections - 35 USC § 102

5. Claims 1-6 remain rejected under 35 U.S.C. 102(b) as being anticipated by Sakuma *et al.* (*Chem. Pharm. Bull.*, 1981, 30(3):810-821, herein, "Sakuma II"). The claims are drawn to a vaccine preparation comprising the adjuvant of claim 1, comprising a saponin compound having a presenegenin skeleton substituted at position 28 with a sugar residue substituted with a trimethozycinnamate residue and a pharmaceutically acceptable carrier, wherein the substituted sugar residue comprises an apiose residue as its substituent when the substituted sugar residue is tetra-substituted. Specifically, the substituted sugar is a sugar residue containing 3 or more carbon atoms. More specifically, the sugar residue is a substituted fucose residue. Also claimed is the compound of claim 1, wherein the saponin compound is prepared from a crude drug.

Applicant's arguments have been fully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following: Applicant argues that Sakuma II does not disclose the actual structure of onjisaponins F and G, but refers to another paper, also authored by Sakuma *et al.* (*Chem. Pharm. Bull.*, 1981, 29(9):2431-2441, "Sakuma I"). Applicant argues that the saponin compound recited in claim 1 includes onjisaponins E, F and G,

while excluding A and B (due to the presence of the trimethoxycinnamate moiety). Applicant argues that the mere disclosure of onjisaponins E, F and G is not sufficient to anticipate the instant claims because the use of the onjisaponins is not disclosed in either of Sakuma I or II.

In response, the Office does not find Applicant's arguments persuasive. The mention of onjisaponins F and G in Sakuma II is sufficient to anticipate the instant claims. While the actual structures of onjisaponins F and G are not drawn as figures in Sakuma II, they are disclosed. Sakuma II discloses that onjisaponins F and G exist and that their structure is already known (in Sakuma I). With regard to Applicant's argument that Sakuma II is not an enabling reference, the Office does not agree. An anticipatory reference need only teach how to make the claimed product. There is no legal requirement that an ancticipatory reference teach how to use the disclosed produce. (*In re Schoenwald*, 964 F.2d 1122, 22 U.S.P.Q.2d 1671 (Fed.Cir. 1992). Therefore, the claims remain rejected as anticipated by Sakuma II.

Claim Rejections - 35 USC § 103

6. Claims 7-9 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakuma II (above) in view of Kensil (*Critical Reviews in Therapeutic Drug Carrier Systems*, 1996, 13(1/2):1-55). The claims are drawn to a vaccine preparation comprising the adjuvant of claim 1, comprising a saponin compound having a presenegenin skeleton substituted at position 28 with a sugar residue substituted with a trimethoxycinnamate residue and a pharmaceutically acceptable carrier, wherein the substituted sugar residue comprises an apiose residue as its substituent when the substituted sugar residue is tetra-substituted. Specifically, the substituted sugar is a sugar residue containing 3 or more carbon atoms. More specifically, the sugar residue

is a substituted fucose residue. The claims are only enabled for vaccines for certain microorganisms, not all the microorganisms listed in claim 9. However, in the interest of compact prosecution, the non-enabled vaccine microorganisms will be treated as immunogenic compositions.

Sakuma discloses the structures of onjisaponins E, F and G, but does not disclose a use for the compounds. However, Kensil reviews the use of saponins (triterpene glycosides from *Quillaja saponaria*) as vaccine adjuvants in inactivated influenza virus vaccines delivered intranasally (page 21, second full paragraph). Kensil also discloses the use of saponins as adjuvants with experimental HIV vaccines (page 22, second paragraph), various bacteria such as *E. coli* (page 24, line 1), *B. pertussis*, *Plasmodium yoelii*, *Toxoplasma gondii* (page 25, part C, "Parasitic Vaccines") and *Schistomona mansoni* (page 26, first full paragraph). It would have been obvious to use the onjisaponins of Sakuma as vaccine adjuvants. One would have been motivated to use them as adjuvants because saponin compounds are used as adjuvants; saponins and onjisaponins have the general saponin structure and have triterpene/triterpenoid structure. One of ordinary skill in the art would have known that saponins were useful as adjuvants, and would have had a reasonable expectation of success that the onjisaponins of Sakuma would have functioned similarly to saponins in general based on Kensil's review and the similarity of their structures. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been fully considered with regard to the rejection under 35 U.S.C. 103(a), but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that structures of the instant claims are completely different from the compounds of Kensil. Specifically, Kensil refers to saponins QS-7, QS-17, QS-18 and QS-21, having a quillaic acid skeleton. The instant claims have a presengenin skeleton.
  - In response, Applicant has not demonstrated that the different structures of presengenin and quillaic acid are expected to act differently. Kensil teaches that saponins, having the triterpene glycosides from *Quillaja saponaria*, are useful as adjuvants. One of ordinary skill in the art would have been motivated to use Sakuma's compound as an adjuvant because it is a saponin, and it has the same triterpene glycosides as the saponins from *Quillaja saponaria.*
- Applicant argues that Kensil teaches away from the instant invention. Kensil discloses that the C4 aldehyde of saponin QS-21 was blocked with small molecules to prevent aldehyde reactivity (page 42, lines 1-15). Kensil teaches that these derivatives were inactive as adjuvants for either stimulation of antibody or CTL response.
  - In response, the Office interprets the passage from Kensil differently than Applicant. Kensil teaches that the derivatives were inactive as adjuvants. Note that the derivatives that Kensil speaks of are saponins having their C4 aldehyde blocked with small molecules. The blocked saponins were inactive as adjuvants. Kensil is not teaching that the saponins (prior to blocking) were ineffective as adjuvants. Kensil's disclosure relates to the discovery of critical groups of the saponins, specifically, quillaic acid.

Therefore, in view of the teachings of Sakuma and Kensil, the invention would have been obvious to one or ordinary skill in the art at the time of the invention.

Conclusion

7. No claim is allowed. Claims 1-9 and 16 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
June 1, 2005

JAMES HOUSEL 6/13/05
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600